

Acute Porphyria Presenting as Epilepsia Partialis Continua

Thi Phuoc Yen Tran^a Karine Leduc^b Martin Savard^b Nicolas Dupré^b
Donald Rivest^c Dang Khoa Nguyen^a

^aService de Neurologie, Hôpital Notre-Dame, Centre Hospitalier Universitaire de Montréal, Montréal, Qué., ^bService de Neurologie, Hôpital de l'Enfant-Jésus, Centre Hospitalier Universitaire de Québec, and ^cService de Neurologie, Hôpital Hôtel-Dieu de Lévis, Centre Hospitalier Universitaire de Québec, Québec City, Qué., Canada

Key Words

Acute porphyria · Status epilepticus · Epilepsia partialis continua

Abstract

Purpose: The porphyrias are a defect in the biosynthesis of heme which can be associated with different neurological symptoms during acute attacks such as peripheral neuropathy, mental disturbance and seizures. So far, there have only been a few case reports of status epilepticus, none of which were of epilepsia partialis continua (EPC). We present here two cases of hereditary coproporphyria (HCP) manifesting EPC as part of the clinical presentation.

Method: The patients' medical charts, EEG and imaging studies were carefully reviewed.

Results: Case 1 is a 49-year-old male who first presented a tonic-clonic seizure. Case 2 is a 30-year-old male who came to the emergency room for a convulsive status epilepticus. Both evolved to EPC over the next days. EPC persisted despite several antiepileptic drug trials. Diagnosis of HCP was confirmed by a high level of urine, fecal and serum porphyrins in both cases and by genetic testing in one. Over the last 3 years, the first patient has continued to present non-disabling EPC and has had four tonic-clonic seizures associated with alcohol consumption. The second patient died from brain edema one month and half after admission. **Conclusion:** Acute porphyrias should be included in the differential diagnosis of new onset status epilepticus, including EPC. Their recognition is important as it modifies significantly patient management, since many anticonvulsants are porphyrogenic.

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Introduction

The porphyrias, a group of disorders characterized by a variable catalytic defect of one of the seven enzymes in the biosynthesis of heme, are classified clinically as acute or non-acute porphyrias based on their clinical manifestations with or without neurovisceral attacks [1–3]. The major manifestations of acute porphyrias are neurological, including neuropathic abdominal pain, peripheral neuropathy, mental disturbance and seizures. Seizures affect 10–20% of patients with acute porphyria [1]. The most commonly reported types of seizures are complex partial seizures and tonic-clonic seizures [4, 5], even though EEG documentation of such seizures have been sparse. Status epilepticus has also been rarely reported. Here, we report two patients with hereditary coproporphyrin (HCP) who presented with status epilepticus and an EEG documentation.

Case Summaries

Case 1

A 49-year-old right-handed man with a past medical history of Berger's disease presented to the emergency room on December 13, 2009, for a 1-min-long tonic-clonic seizure and increasing confusion over the past week. He was immediately started on acyclovir and phenytoin. The initial EEG, brain MRI and lumbar puncture were normal. Within 2 days, he developed continuous right hand myoclonic jerks compatible with epilepsy partialis continua (EPC). Repeat brain MRI performed 3 days after admission disclosed non-enhancing high T2 and FLAIR signal changes over the bilateral temporal lobes (fig. 1). Brain PET revealed focal hypermetabolism over the bilateral frontal and temporal lobes, predominantly over the left side. Repeat EEG revealed left frontotemporal periodic lateralized epileptiform discharges (fig. 2). A repeat lumbar puncture at day 3 was within normal limits. Bacteriological, viral serological (including herpes simplex virus PCR) workup, immunologic parameters as well as toxicology screen revealed no abnormal findings. While the confusion progressively waned, EPC persisted despite several antiepileptic drug trials (phenytoin, valproic acid, carbamazepine, clobazam, lamotrigine). A probable diagnosis of HPC was eventually made when urine coproporphyrins and fecal total porphyrins returned to twice the normal range (even when testing was made 9 days after admission while the patient was improving). These abnormal results could not be explained by other conditions which have previously been associated with secondary coproporphyrinurias such as abuse of toxic substances, liver diseases, malignancies, diverse hematological diseases, etc. [6]. Over the last 3 years, the patient has continued to present non-disabling EPC (manifesting only as very low-amplitude right hand myoclonic jerks) and has had a total of four tonic-clonic seizures in the context of alcohol consumption. He remains with mild memory problems and is currently treated with levetiracetam. On the last brain MRI (2 years after initial setting), T2 signal changes had decreased significantly (fig. 3).

Case 2

A 30-year-old man, known only for a generalized anxiety disorder, was brought to the emergency room on November 16, 2011, in convulsive status epilepticus preceded over the last 3 days by nausea, vomiting and headaches. Initial management included intravenous benzodiazepines and phenytoin followed by intubation and a perfusion of midazolam and propofol. The patient then evolved to EPC as he presented continuous left hand and mouth myoclonic jerks, very rarely associated with altered consciousness. EEG (fig. 4) showed

diffuse slowing, sometime associated with right frontotemporal periodic lateralized epileptiform discharges. MRI disclosed right hemispheric gyriform increased signal on T2-weighted images, restricted diffusion on DWI/ADC images and mild midline shift to the left. Brain PET revealed focal hypermetabolism over the right frontal and temporal lobes, and to a lesser extent in the right occipital region. Two lumbar punctures were normal. As in the first patient, bacteriological, viral serological workup as well as immunologic parameters failed to disclose a plausible cause. His condition eventually worsened, with decreased level of consciousness leading to intubation, despite large spectrum antibiotics, acyclovir, several antiepileptic drug trials (phenobarbital, levetiracetam, lacosamide, topiramate, vigabatrin, gabapentin) and immunotherapy (intravenous immunoglobulins, plasma exchanges). Diagnosis of porphyria was made when results from urine, fecal and serum porphyrins returned elevated at 3 weeks after admission. One month and a half after admission and despite hematin therapy and withdrawal of porphyrinogenic drugs, the patient eventually died from brain edema secondary to the status epilepticus, after he had suffered a porphyric attack from an isoflurane trial. Later, genetic testing confirmed HCP with a rare homozygous missense G189S mutation in the coproporphyrinogen III oxidase gene.

Discussion

Porphyrias are uncommon, complex metabolic disorders caused by deficiencies in the activities of the seven out of eight enzymes of the heme biosynthetic pathway [3]. They are generally subdivided into acute and non-acute porphyrias on the basis of their major clinical manifestations [3]. The acute porphyrias are well-defined genetic disorders of heme biosynthesis characterized by acute life-threatening attacks of nonspecific neurologic symptoms. These acute porphyrias are comprised of acute intermittent porphyria (AIP), HCP, variegate porphyria (VP) and 5-aminolevulinic acid dehydratase porphyria (ADP) in which AIP is the most frequent type. The combined prevalence of the acute porphyrias is approximately 5 cases per 100,000 persons, they are more common in women than in men, and often generally develop during adult life. Acute porphyric attacks can be exacerbated by a variety of factors, including porphyrinogenic drugs, alcohol, endogenous hormones particularly progesterone, pregnancy, cigarette smoking, metabolic stress induced by infections or surgery and reduced caloric intake [1]. Misdiagnoses of porphyrias are common because the signs and symptoms of acute attacks are variable and may mimic many other diseases. They can present with acute neurovisceral attacks, which may be accompanied by skin lesions in HCP and VP. Abdominal pain [1], reported approximately in 85–95% of patients, is often accompanied by nausea, vomiting, constipation and diarrhea. Other symptoms include acute psychiatric symptoms, seizures, tachycardia and hypertension, and peripheral neuropathy.

Seizures [1] occur in approximately 10–20% of patients with symptomatic porphyrias. The most common types of seizures reported in the literature consist of complex partial or tonic-clonic seizures. Status epilepticus is less common, having been reported on five instances only. A summary of these previously reported cases is presented in table 1 [6–10] along with our cases. All were adult patients. Status epilepticus was part of the initial presentation for all subjects with the presence of visceral symptoms in two. Pregnancy was a precipitating factor in two. The type of status varied greatly from convulsive status epilepticus to non-convulsive status epilepticus, complex partial status and EPC. EEG revealed non-specific periodic discharges or rhythmic focal activity. Non-surprisingly, confirmation of diagnosis led to modification of the treatment regimen with good outcome

for all patients except one (case 2). Out of the previously five reported cases, 3 patients had AIP, 1 patient had VP and 1 had an unknown type of acute porphyria, while both of our patients had HCP.

Current understanding of the pathogenesis of seizures suggests the hepatic production of a neurotoxic substance, presumably ALA [a γ -aminobutyric acid (GABA) analogue] and/or PBG which may interact with GABA or glutamate receptors [2]. A combination of endothelial dysfunction, hypoperfusion, and vasoconstriction in this setting of neurotoxicity can lead to a compromise of the blood-brain barrier and brain edema [11]. MRI may help detect changes occurring in the brain at the time of the acute attack though lesions are non-specific (cortically and/or subcortically, anterior or posterior, without or with mild enhancement, generally but not always reversible) [11, 12]. Seizures, when they occur, are a therapeutic challenge because most AEDs (phenobarbital, carbamazepine, clonazepam, phenytoin, primidone, ethosuximide, valproic acid, lamotrigine, felbamate, tiagabine, topiramate) may exacerbate attack of acute porphyria [13]. Drugs reported to be relatively safe include gabapentin [6, 8, 14], levetiracetam [7], and possibly oxcarbazepine [15].

Conclusion

Acute porphyrias may be a cause of new onset convulsive status epilepticus and EPC. Although rare, their recognition is important as it modifies significantly patient management and probably their outcome.

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Table 1. Summary of clinical, imaging, and encephalographic features of previously reported cases and our cases

	In the literature					Our patients	
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age, years	42	48	26	22	22	49	30
Gender	female	female	female	female	female	male	male
Past medical history	epilepsy related to L F astrocytoma (resected 5 y earlier)	AIP diagnosed at age 20 after refractory SE; 3 other SE subsequently	none but family history of AIP	normal first pregnancy	normal first pregnancy	Berger's disease	generalized anxiety disorder
Exacerbating factors	surgery for presumed cholecystectomy	leg deep venous thrombosis	alprazolam	second pregnancy	second pregnancy	ROH	–
Visceral symptoms	abdominal discomfort, anorexia, episodic dark urine	–	–	–	–	–	nausea, vomiting
Neurological symptoms	delirium, complex partial SE	refractory complex partial SE	confusion, quadriparetic, labored respiration, convulsive SE	delirium, GTC seizure → convulsive SE	psychiatric symptoms GTC seizures → convulsive SE	confusion, one GTC seizure → EPC	headache, confusion, convulsive SE → EPC → NCSE
Seizure description	staring, altered consciousness, complex motor behavior	R head deviation, R facial clonic jerks, R arm tonic-clonic activity, 20–120 s, ~15 to 20/h	R facial and upper limb twitching (day 12) → convulsive SE (day 14)	loss of consciousness, R leg clonic activity → R arm → GTC activity, 2–3 min → convulsive SE	–	tonic-clonic seizure evolving into continuous right hand myoclonic jerks	four GTC seizures → NCSE with the L hand and mouth jerks, rarely associated with altered consciousness
MRI/scan	unchanged postoperative encephalomalacia	CT: possible L hemisphere edema	–	biF ↑ diffusion coefficient	–	biT T2/FLAIR	R hemispheric gyriform T2 changes + diffusion restriction; mild L midline shift
EEG	bursts of spikes, poly-spikes, sharp waves, ±sharp/slow complexes over biFT leads L R	L>R slowing; during seizures: rhythmic L FT theta activity	–	during seizures: rhythmic L F slow activity → both hemispheres	–	L F PLEDs	severe diffuse slowing; R FT PLEDs
Treatment before diagnosis	PHT, CBZ, LZP, Pentobarbital	–	–	LZP, PHT, LEV	OXC, LEV, PHT	acyclovir, PHT, VPA, CBZ, CLB, LTG	antibiotics, acyclovir, plasma exchange, IG, Pb, propofol, LEV, LCM, TPM, VGB,
Treatment after diagnosis	high carbohydrate diet, hematin, GPN	hematin; GPN; OXC → LEV + Mg	hematin, propofol, GPN	GPN, LZP, high carbohydrate intake, hematin, abortion	abortion	LEV	hematin, (VGB, LEV, LCM) → GPN, plasma exchange, IG
Outcome	no further delirium over next 2 years; modest ↓ in seizure frequency	no further seizures over next 8 months of FU	convulsions stopped, alert, able to walk with support (day 16)	no further convulsion after abortion	no further seizures as well as attack of hepatic porphyria over next 2 years of FU	mild memory deficits, persisting but non-disabling R hand EPC; 1 GTC seizure and 1 cluster of 3 GTC seizures in the setting of ROH intake over last 3 years	deceased
Type of porphyria	AIP	AIP	AIP	VP	acute hepatic porphyria	HCP	HCP
Reference	Yandel and Watter (1995) [7]	Zaatreh et al. (2005) [8]	Pandey et al. (2003) [9]	Engelhardt et al. (2004) [10]	Weinzierl et al. (2007) [11]		

L = Left; R = right; F = frontal; T = temporal; PHT = phenytoin; CBZ = carbamazepine; Pb = phenobarbital; LZP = lorazepam; GPN = gabapentin; SE = status epilepticus; NCSE = non-convulsive status epilepticus; PLEDs = periodic lateralized epileptiform discharges; GTC = generalized tonic-clonic; IG = immunoglobulin.

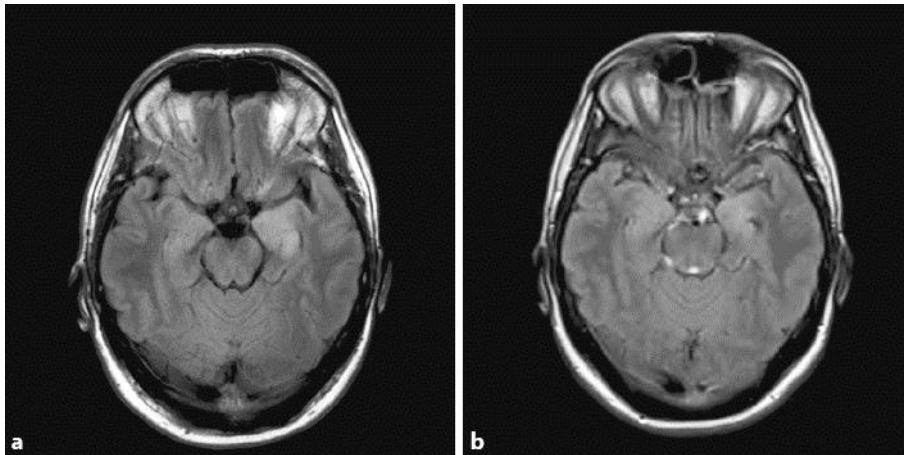


Fig. 1. FLAIR sequence showing hyperintensity over both mesial temporal structures (a), with mild incomplete regression after 2 years (b).

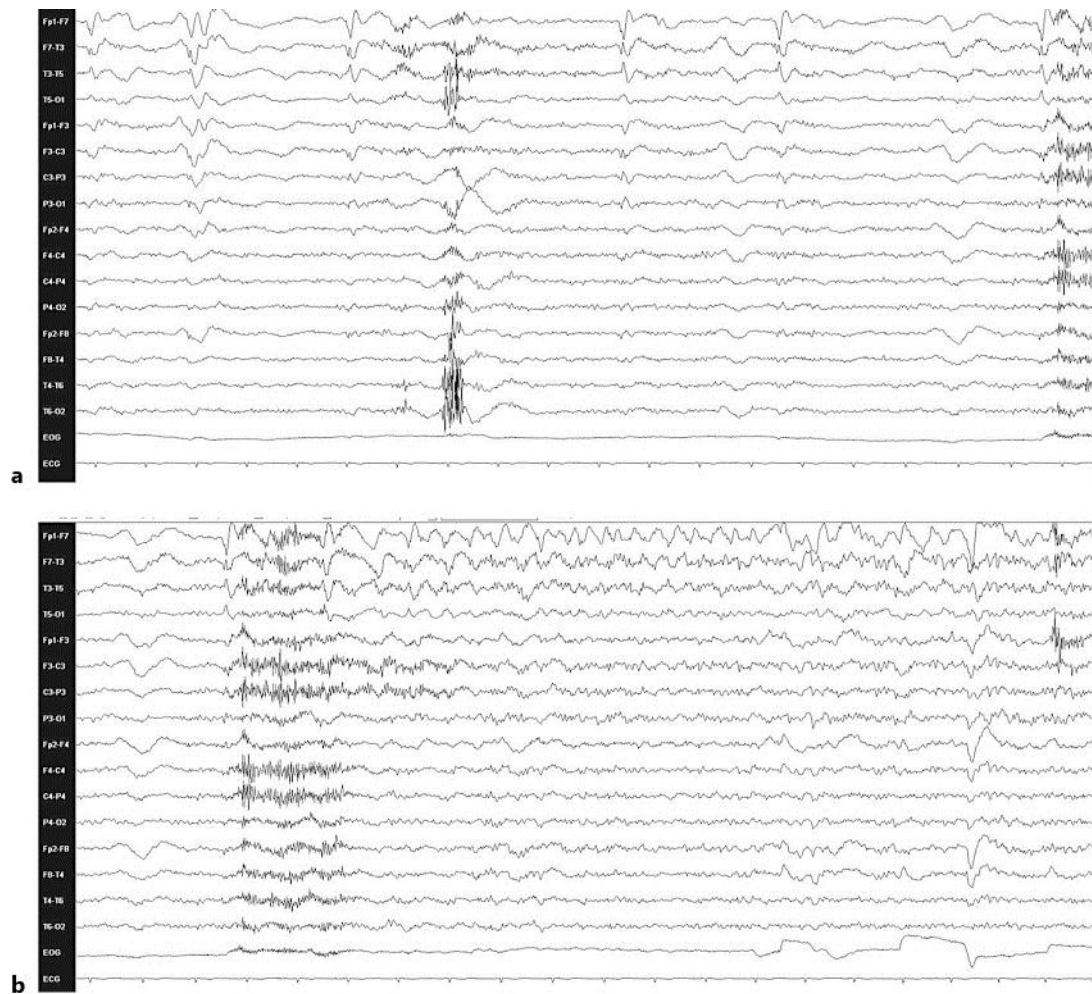


Fig. 2. **a** EEG with left frontotemporal periodic lateralized epileptiform discharges. **b** Left frontotemporal periodic discharges evolving into rhythmic slow activity discharge most prominent over the left frontotemporal region (HFF = 35 Hz; LFF = 1 Hz).

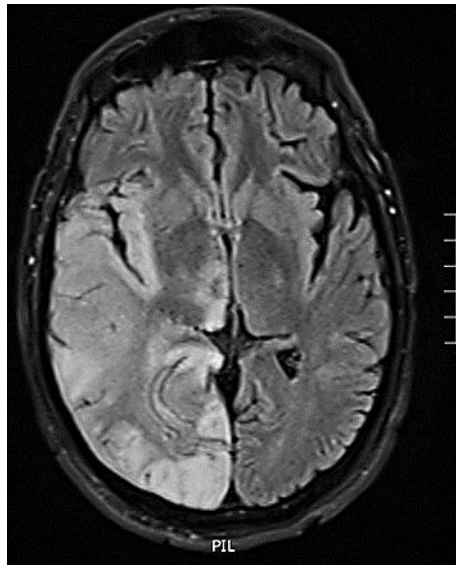


Fig. 3. FLAIR image showing right hemispheric gyriform hyperintense signal changes.

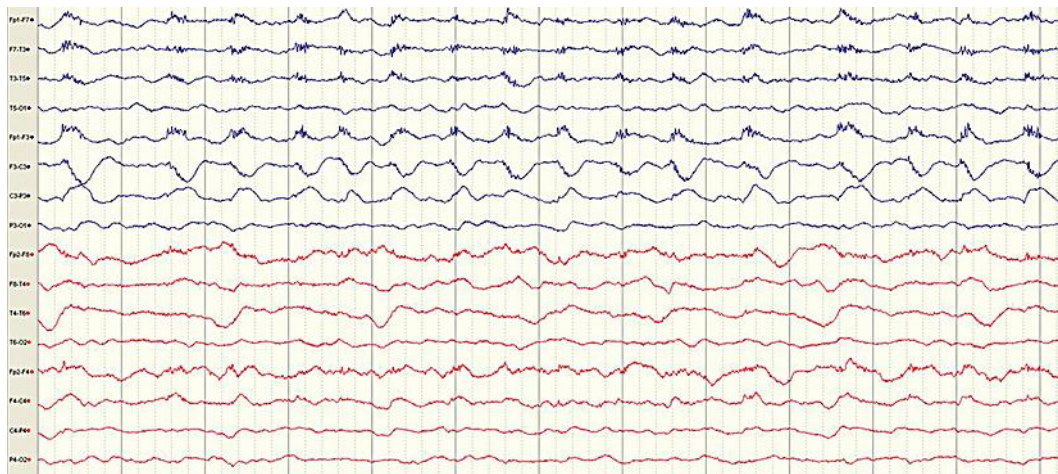


Fig. 4. EEG showing diffuse slowing activity, right frontal subtle/blunted periodic lateralized epileptiform discharges and left-sided muscle artifacts due to left facial jerks.